peptide wherein from one to four of the residues in AA413-AA435 are conservatively substituted, inserted or deleted.

C4 2. (Amended) An IgE-CH3 domain antigen peptide of claim 29 selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:84.

C5 19. (Amended) A peptide conjugate comprising a carrier protein covalently attached to one or more IgE-CH3 domain antigen peptides according to claim 29.

Attached is a copy of the marked up claims as Appendix A.

REMARKS

The specification has been amended to correct formatting and printing errors caused by the computer software.

A paragraph has been inserted to provide information of related applications as required by the Examiner. The present application is a continuation-in-part application of US application Serial No. 09/100,287, filed June 20, 1998 and was filed as an international application under the Patent Cooperation Treaty on June 21, 1999 and claims priority to US application Serial No. 09/100,287, filed June 20, 1998. Applicant is entitled to claim of priority of June 20, 1988, June 20, 1999 being a Sunday.

Claim 1 has been replaced with claim 29 to more clearly and distinctly state the claimed invention. Support for the amendment is found in the specification on page 26, lines 27-32, Table 1; page 35, line 21 to page 36, line 11. No new matter is entered hereby. Entry of the amendment is requested.

RESPONSE

The response is set forth in accordance with the paragraphs in the Office Action.

1-4. Restriction Requirement

Applicants request modification of the restriction requirement to include claims 3-18, 20-25 in the present application. The restriction requirement presently imposed is arbitrary and inconsistent with the Examiner's position that peptides and

peptide conjugated to carrier proteins may be examined in one application. Further, the restriction requirement is not reasonably related to the burden of search and examination.

Reconsideration of the restriction is requested for the reasons stated in the response to the restriction requirement dated March 20, 2002 and the reasons stated below.

The Examiner has restricted the present application to Clams 1-2 and 19-20. Claims 1-2 are directed to an IgE-CH3 domain antigenic peptide selected from the group consisting of SEQ ID NOs: 5, 6, 7, 8 and 84, homologues of these peptides and analogs of these peptides. Claims 19 - 20 are directed to the conjugation of the IgE-CH3 domain antigenic peptide with a carrier protein. Presently, claim 1 has been replaced with claim 29. The present response is made as if the rejection of claim 1 applies to amended claim 29.

It is clear that the present invention is directed to the use of AA413-AA435 of mammalian IgE as an antigenic peptide to elicit antibodies that inhibit the binding of IgE to basophils and mast cells. The elicitation of such antibodies by the claimed IgE-CH3 domain antigenic peptide is enabled by conjugation to a carrier protein or to T-helper epitopes. It is clear that the Examiner considers that the claims to the IgE-CH3 domain antigenic peptide and the claims wherein the IgE-CH3 domain antigenic peptide is conjugated to a carrier protein such as KLH can be included in the same application.

Applicant wishes to point out that the conjugation of the IgE-CH3 domain antigenic peptide with a carrier protein is to utilize the T-helper epitopes in the carrier protein to present the IgE-CH3 domain antigenic peptide to the B-cells for eliciting the production of antibodies to the IgE-CH3 domain antigenic peptide. Thus the conjugation of the claimed peptide to the carrier protein is identical in purpose for conjugating claimed peptide to a T-helper epitope and/or an invasin domain. Yet, the Examiner considers the conjugation of the IgE-CH3 domain antigenic peptide with T-helper epitopes and/or an invasin domain peptide to be a different invention. This position is arbitrary, inconsistent and unreasonable.

Moreover, the restriction excluding claims 3-18 and 21-22 is not reasonably related to the burden of search or examination. Once the IgE-CH3 domain antigenic peptide with the sequence AA413-AA435 of IgE modified with terminal cysteines is found to be novel and unobvious, no further search is necessary to determine whether these same peptides conjugated to T helper epitopes and/or invasin domain peptide are novel or unobvious. Therefore, claims 3-18 directed to the claimed peptides conjugated to T helper epitopes should be included in the present application. Moreover, claims 21 and 22 directed to a polymeric form of the IgE-CH3 domain antigenic peptide and claims 24 and 25 directed to a pharmaceutical composition comprising IgE-CH3 domain antigenic peptide should be included in the same application for the reasons stated..

It is clear that the claims 1-25 define inventions that are linked to form a single general inventive concept, the identification of an immunogenic epitope in IgE-CH3 domain and the use of the epitope as a cyclized peptide to elicit antibodies in situ to inhibit the binding of IgE to basophils and mast cells. Therefore, applicant request the inclusion of claims 3-18, 20-25 in the present examination. The restriction requirement as presently imposed should be withdrawn.

5. Objection to reference to a website on pages 4, 25, and page 44.

The Examiner objected to the reference to the website http:/www/pdb.bnl.gov/pdb.bin/pdbids on pages 4, 25 and 44 as a hyperlink. Applicant wishes to point out that this reference was not presented as a hyperlink, which requires a special tag. The website address was presented for information purposes and to provide a convenient way for the Examiner to access the cited information on the Internet. A copy of the cited reference has been provided in the Information Disclosure Statement. The inclusion of such information is required by Rule 56 which imposes an obligation on the Applicant to provide information that may be material to the determination of patentability. Therefore, the objection should be withdrawn.

6 & 7. Cross reference to related applications

The Examiner required the inclusion of a paragraph on the relation of the present application to PCT application no. PCT/US99/13959. A paragraph entitled

CROSS REFERENCE TO RELATED APPLICATIONS has been inserted to indicate that this is a continuation-in-part application of earlier filed application, serial no. 09/100.287.

This application is the national phase of PCT application no. PCT/US99/13959. The claim to priority was asserted during the proceedings before the PCT office. It is believed that under PCT rules, the Patent Office has provided a copy of the priority application to WIPO and it is not necessary for Applicants to do so. This was acknowledged by the Examiner in the interview.

9. Rejection of claims 1 and 19-20 under 35 U.S.C. §112

Claims 1 and 19-20 dependent thereon were rejected under §112, first paragraph for lack of enablement. Reconsideration of the rejection in view of the replacement of claim 1 with claim 29 is requested.

It appears that the Examiner has interpreted claim 1 as filed as being directed to any homolog or any analog of an unspecified peptide derived from IgE. It was not the intention of the Applicants to claim any homolog or any analog of an unspecified peptide derived from IgE. As originally presented, claim 1 is directed to a specific IgE-CH3 domain antigen peptide and a homolog and an analog of the specified IgE-CH3 domain antigen peptide. Nevertheless, because of the tendency to read the words "homolog" and "analog" in isolation from the word "thereof", which means that the homolog or analog is of the specified and claimed peptide, Applicant has rewritten claim 1 as claim 29.

Claim 29 is directed to an antigenic peptide corresponding to AA413-AA435 of mammalian IgE-CH3 with terminal cysteines inserted by modification or as in the natural sequence. It is clear that this is supported by the disclosure, in particular, page 35, line 21 to page 36, line 11. The specific examples of mammalian IgE-CH3 are from humans, dogs, rats, mice and horses. The specification clearly taught at

page 4, lines 1-21;

page 20, line 22- page 21, line 33;

Table 1;

page 25, line 13 to page 27, line 2;

page 35, line 21 - page 36, line 25;

page 36, line 27-page 37, line 2;

how to locate the particular segment of the IgE-CH3 domain protein from mammalian IgE. Based on this written description, it is very easy for any person of skill in the art to identify AA413-AA435 from any mammalian IgE sequence, take a look to see if a cysteine is at either terminal of AA413 or AA435 and modify the sequence by adding a cysteine if a terminal residue is not a cysteine.

The specification at page 37, line 21 to page 38, line29 clearly describes how to synthesize the claimed IgE-CH3 domain antigenic peptide and conjugate it to a carrier protein or a T helper epitope and then use it to immunize an animal to elicit the desired antibodies.

The description is further substantiated and supported by experimental data. Example 1 clearly describes the identification of the particular segment of IgE-CH3 domain from several mammalian species and the testing of the segments to demonstrate the effective immunogenicity of the claimed peptide. The synthesis of the constructs using the Bruce Merrifield synthetic peptide procedure. The conjugation of the claimed IgE-CH3 domain antigenic peptide to a carrier protein or a T helper epitope with appropriate linkers.

Example 2. describes the immunization of guinea pigs with the conjugated peptides, the testing of the serum for antibodies that are clearly shown to inhibit binding to basophils and mast cells.

Although the specification named specific IgE sequences from humans, dogs, mice, rats and horses as examples, it is clear that the claimed IgE-CH3 domain antigenic peptide can easily be identified from all mammalian IgE, a known antibody of which many of the sequences known. Applicants only presented five sequences because it would be too voluminous to present the IgE sequences of all mammalian species.

Under the law, enablement is determined based of whether there is sufficient information provided in the specification to a person of skilled in the art to make and use the claimed invention. The present invention is in the field of immunology.

Thus, the standard is based on a person of skill in the art in immunology, who would have good knowledge of proteins and peptides. In this case, the specification clearly described the class of mammalian IgE as the basis on which the claimed IgE-CH3 domain antigenic peptide can be derived. Five mammalian IgE sequences were provided as members of this class. The Examiner has not shown any evidence that a person of skill in the art would not be able to identify the claimed peptide from other mammalian IgE based on the description provided.

The Examiner cited In re Wands to support the lack of enablement rejection. The claimed subject matter in In re Wands is an immunoassay method for the detection of hepatitis B surface antigen by using high affinity IgM antibodies. The Board in that case had rejected the claimed invention because the Applicants had not shown that all of the hybridomas would secret the antibodies that are useful in the method and that it would be undue experimentation to screen the antibodies produced to determine whether they are effective. The Court of Appeals for the Federal Circuit reversed the rejection. The Court clearly stated that undue experimentation cannot be based on the number of experiments that may be necessary. If the screening test is one that is known and done routinely by those skilled in the art, then the experimentation is not undue. The holding in In re Wands clearly supports Applicants' position that the description of the method of identifying AA413-AA435 of IgE as an antigenic peptide, the synthesis of the claimed peptide and the testing thereof to show that these peptides are immunogenic enables the claimed invention.

The decision in In re Wands clearly contradicts the contention of the Examiner that the claimed invention is not enabled. Moreover, the claimed subject matter of the present case are peptides with a particular sequence and not antibodies or the use of the antibodies produced. The claimed peptide corresponds with a specific segment of the IgE and has been shown to be effective for eliciting antibodies that are effective in inhibiting the binding of IgE to basophils and mast cells. An IgE is an IgE no matter which species it came from. Although the sequence may vary, a person with skill in the art would be able to identify AA413-AA435 of IgE. It merely requires alignment of the specific IgE sequence with that published for human IgE and count to AA413 to AA435.

It is also known to a person skilled in the protein art and immunology that each protein comprises segments with specific biological functions, some of which are known as B-cell epitopes or T-cell epitopes, etc. Once a segment from a protein has been identified as an effective epitope, it remains effective as an epitope no matter which species the protein came from. This is the molecular basis of biological function based on the structure of the protein. It is predictable and certain and not unpredictable as stated by the Examiner.

The Examiner contends that there is unpredictability but did not shown from the prior art references what is unpredictable about the identification of such epitopic segments. In fact, all of the references indicate that to those of skill in the art of immunology, once a segment of a protein is identified as being an epitope, it remains as an epitope no matter which mammalian species the protein is from. There is nothing to predict. Therefore, the rejection based on lack of enablement is wrong and should be withdrawn.

The Examiner contends that claim 1 was directed to any homolog from the epsilon heavy chain of any mammalian IgE. Applicants would like to point out that claim 1 as presented was directed to homologs thereof, with "thereof" pointing to SEQ ID NOs: 5, 6, 7, 8 and 84 derived from mammalian IgE. Claim 1 was not directed to any homolog of the epsilon chain of IgE. However, to avoid any disputes, claim 1 has been replaced with claim 29 which recites the use of AA413-AA435 of mammalian IgE so that the use of the offending word homolog has been rendered unnecessary. The scope of the claims remains the same. Thus, as presented claim 29 is enabled, and the rejection on this basis should be withdrawn.

The Examiner also contend that analogs of the claimed peptides are not enabled citing Ngo et al to shown that conservative substitutions, addition or deletion in a protein will require guidance because of the difficulty of determining protein folding and tertiary structure. However, the present claim 29 and claims dependent thereon are directed to a short peptide of 23 amino acids which are cyclized by the terminal cysteines. There is no folding or tertiary structure to determine or maintain. Applicants have shown that substitutions of cysteines with serines works. On page 19, lines 1-9, the specification showed the possible substitutions of amino acids in a

15 residue peptide. Asp may be substituted with Glu, Leu may be substituted with Ile, Val, Phe, Lys may be substituted with Arg without affecting the immunological function of a peptide. Other such conservative substitutions such as alanine with glycine or serine; proline with hydroxyproline, lysine with ornithine etc. would not generally alter the biological function of a peptide or protein. Applicants also demonstrated that the substitution of Cys with Ser at AA 418 did not affect the immunogenicity of the claimed peptide. The specification also described polymeric forms of the claims peptides and the addition of cysteines in the terminal positions. See page 38, line 14 to page 39, line 16. Clearly, analogues of the claimed peptide AA413-AA435 of IgE is enabled. The rejection of the claims for reciting analogues of the claimed peptide should be withdrawn.

10. Rejection of claims 1, 19 and 20 for lack of sufficient description

The Examiner further rejected the claims for lack of sufficient disclosure of any homolog and any analog that is cross reactive and immunologically functional. As stated above, claim 29 is not directed to any homolog or any analog. Only AA413-AA435 of mammalian IgE-CH3 is specified. For the stated above, Applicants believe that the specification fully describe the invention of claim 29.

Claim 29 is directed to AA413-AA435 of mammalian IgE circularized by the modification of the terminal ends of the peptide with cysteines. The specification clearly describes a peptide that corresponds to AA413-AA435 of various mammalian IgE, including that of human IgE, dog IgE, mice IgE, rat IgE and horse IgE. See for example, page 36, line 27 to page 37, line 2.

The law requires that the specification sufficiently describes the claimed invention such that a person of skill in the art understands that Applicants is in possession of the claimed invention. The Federal Circuit has stated that whether the written description is sufficient is a factual issue. Vas-Cath v. Mahurkar, 935 F2d 1555 (Fed. Cir. 1991) It was held that the drawings of a design application provided sufficient description to support claims for a utility patent. See also In re Alton et al. 37 USPQ 2d 1578 (Fed. Cir. 1996) Claims directed to human gamma interferon analogs were found to be supported by the specification wherein a claimed analog with cys1, tyr2 and cys3 deleted and Met substituted with Met to be supported by an

analog described in the specification wherein there was a further substitution of lys81 with asparagine.

In the present case, Applicant had described analogs with substitutions, and additions. For example in Table 2, Cys418 was substituted with Ser and the addition of Cys at the terminals of the peptide or the addition of Gly-Gly as linking residues. It is believed that the specification fully met the written description requirement and the rejection on this basis should be withdrawn.

The Examiner cites University of California v. Eli Lilly for the proposition that Applicants are not in possession of the claimed homologs and analogs. This case is directed to a claim for human DNA for insulin. The specification did not provide the DNA sequence for human insulin. The CAFC held that the description of mouse DNA for mouse insulin does not provide sufficient written description of human DNA. The decision in UC v. Lilly is inapposite. The present case is not about DNA, which is not a protein or a peptide. DNA encodes a protein and provides the template for the expression of a protein. Applicants believe that DNA are entirely different from a peptide. Moreover, unlike a protein with specific biological functions residing in specific segments, DNA does not have the same specific biological functions. Thus, mice DNA sequence is not predictive of the human DNA sequence.

Moreover, as presented claim 29 is directed to a specific segment of mammalian IgE and immunologically functional analogs of the specific segment. As shown above, there is ample written description to show that Applicants are in possession of the claimed invention.

11 & 12 Rejection under 35 U.S.C. §112, second paragraph.

Claims 1-2 and 19 and 20 were rejected as indefinite for reciting "IgE-CH3 domain antigen peptide" and "immunologically functional".

Claim 1 has been cancelled. Claim 29 recites an IgE-CH3 domain antigen peptide with the sequence of AA413-AA435 of mammalian IgE. This is clear and definite.

The Examiner further contends that immunologically functional is ambiguous in that histamine release would be considered immunologically functional. As

presented, claim 29 recites that the antigenic peptide is useful for eliciting antibodies that inhibit binding of IgE to basophils and mast cells. It is believed that as presented claim 29 is clear and definite. Therefore, the rejection on this basis is moot.

13.-15. Rejection of the claims under 35 U.S.C. §102 as being anticipated

The Examiner rejected claim 1 as being anticipated by Navarro et al.

A review of Navarro et al. shows that it described the entire IgE molecule of 616 amino acid residues, how to clone and express the entire IgE. Claim 1 has been replaced with claim 29, directed to AA413-AA435 of the IgE with two cysteines at the termini of the peptide. There is no description, teaching or suggestion that a peptide corresponding to AA413-AA435 of the IgE with two cysteines at the termini can be used to produce antibodies that inhibit the binding of IgE to bashophils and mast cells.

Under the law, the reference must teach each and every element of the claimed invention before anticipation can be found. Each and every element includes the teaching of the absence of a particular feature of the prior art. Navarro et al. does not teach, describe or suggest any of the other amino acids may be omitted. Thus, Navarro et al. cannot be regarded as an anticipation of claim 29, 2, and 19-20. The rejection on this basis should be withdrawn.

The Examiner further rejected claims 1-2 and 19-20 as being anticipated by Gharderi et al.

As admitted by the Examiner, Gharderi et al. describes immunologically functional peptides Y137, AA364-AA383, and Y136, AA 401-AA415 of IgE. There is no teaching, description or suggestion of the peptides of claims 29 or 2, or 19-20, to AA413-AA435 of the IgE with two cysteines at the termini of the peptide.

Since Gharderi et al does not describe, teach or suggest every element of the claimed invention, anticipation cannot be found. The rejection on this basis should also be withdrawn.

16. -17. Rejection of the claims under 35 U.S.C. §102 (e) as being anticipated

The Examiner cited US 6,025,468A as teaching SEQ ID NO:95 as anticipating the claimed peptides. Applicants wish to point out that the present application enjoys an effective filing date of June 20, 1998. The parent application Serial No. 9/100,287 was filed on the same day, June 20, 1998. The claimed peptide of claim 29 and the claims that depend thereon was clearly described in the parent application and, therefore, enjoys the effective date of June 20, 1998. Therefore, US 6,025,468A is not available as a reference under 35 U.S.C. §102 (e). The rejection on this basis should be withdrawn.

The claims were also rejected citing US 6,228,987B. As stated above, the claims of the present application enjoy an effective date of June 20, 1998 and US 6,228,987B is not available as a reference under 35 U.S.C. §102 (e). Similarly, the rejection on this basis should be withdrawn.

18 - 21 Rejection of claims 1, 19 and 20 under 35 U.S.C. §103

Claim 1 was rejected as being obvious over Navarro et al in view of Gharderi et al.

Reconsideration of the rejection is requested.

As stated above, Navarro et al. described the cloning of IgE and the possible use of antibodies to IgE to inhibit binding of IgE to basophils and mast cells. There is no description, teaching or suggestion of the use of a peptide to obtain antibodies that inhibit binding of IgE to basophils and mast cells.

Gharderi et al. described Y136 and Y137 as peptides that may be useful for providing antibodies that inhibit binding of IgE to basophils and mast cells. There is no teaching, description or suggestion of the specific peptide claimed, AA413-AA435 of the IgE with two cysteines at the termini of the peptide. The teaching of Y136 and Y137 representing AA362-AA415 of IgE and AA364-AA383 of IgE as being antigenic teaches away from the claimed invention.

Under the law, to show prima facie obviousness, it is the burden of the Examiner to show that the invention claimed was taught or suggested by the

references cited. Since neither Navarro et al. nor Gharderi et al. suggested the use of the specific peptide claimed, AA413-AA435 with two cysteines at the termini of the peptide, prima facie obviousness has not been shown. The rejection on this basis should be withdrawn.

The Examiner further rejected claim 1, 19-20 as being obvious over Navarro et al. in view of Harlow et al.

The disclosure of Navarro et al. is discussed above. Harlow describes the conjugation of a peptide to KLH with a linker. Navarro et al. does not teach, describe or suggest a peptide. It describes the cloning of IgE with 626 amino acids. Conjugation of KLH to IgE does not arrive at the conjugation of AA413-AA435 with two cysteines at the termini of the peptide conjugated to KLH. Therefore, the rejection of claims 1, 19-20 as being obvious is not in compliance with the law and should be withdrawn.

The Examiner has indicated that SEQ ID NOs: 6-8 and 84 are free of the art. Applicant wish to point out that claim 29 is generic to SEQ ID NOs: 6-8 and 84. SEQ ID NO: 5 should also be free of the art as stated above. Therefore, it is believed that the claims as presented should be allowable.

Applicants wish to thank the Examiner and her Supervisor, Christine Chan for the courtesy and time spent to extensively discuss the invention claimed. During the discussion, Applicants' attorney suggested the replacement of claim 1 with claim 29. It was agreed that if no new matter issues are raised by the rewriting of claim 1 as claim 29, many of the issues raised would be overcome. Applicants have shown that claim 29 is amply supported by the specification and no new matter has been raised. It is believed that the discussion has been of great assistance in the process.

The invention claimed is being commercialized and is of utmost importance to the Applicants. Enclosed herewith is a copy of a manuscript of an article showing the effectiveness of the claimed invention for the treatment of allergies. The paper has been subjected to peer review and approved for publication in Vaccine. Please note that the invention has been regarded highly by both the College of Veterinary Medicine of the North Carolina State University and John Hopkins Asthma and

Allergy Center, who agreed to collaborate with the inventors to test the invention in animals.

It is hoped that the Examiner will agree to examine claims 13-18 and 20-25 with the present application and grant an early allowance.

Respectfully submitted,

Dated: January 10, 2003

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APPENDIX A

MARKED UP CLAIMS

29. (New) An IgE-CH3 domain antigen peptide useful for eliciting antibodies that inhibit the binding of IgE to basophils and mast cells said peptide is about 25 and about 29 amino acids in length cyclized with two cysteine residues separated by about 23 amino acid residues, the sequence of said peptide corresponds to AA413-AA435 of the episilon heavy chain of a mammalian IgE-CH_3 and an analogue of the peptide wherein from one to four of the residues in AA413-AA435 are conservatively substituted, inserted or deleted.

2. (Amended) An IgE-CH3 domain antigen peptide of claim [1] 29 selected from the group consisting of SEQ ID NO:5, SEQ ID NO:6, SEQ ID NO:7, SEQ ID NO:8, and SEQ ID NO:84.

19. (Amended) A peptide conjugate comprising a carrier protein covalently attached to one or more IgE-CH3 domain antigen peptides according to claim [1] 29 .